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Visible-Light-Induced *ortho*-Selective Migration on Pyridyl Ring: Trifluoromethylative Pyridylation of Unactivated Alkenes

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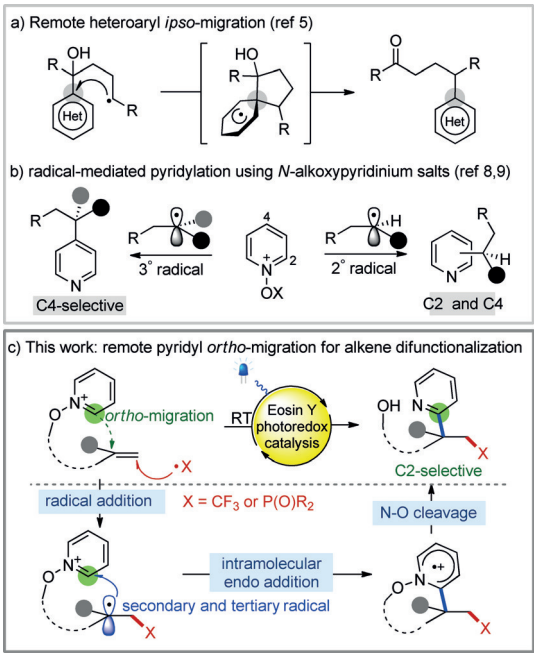
Abstract: *The photocatalyzed ortho-selective migration on a pyridyl ring has been achieved for the site-selective trifluoromethylative pyridylation of unactivated alkenes. The overall process is initiated by the selective addition of a CF_3 radical to the alkene to provide a nucleophilic alkyl radical intermediate, which enables an intramolecular endo addition exclusively to the ortho-position of the pyridinium salt. Both secondary and tertiary alkyl radicals are well-suited for addition to the C2-position of pyridinium salts to ultimately provide synthetically valuable C2-fluoroalkyl functionalized pyridines. Moreover, the method was successfully applied to the reaction with P-centered radicals. The utility of this transformation was further demonstrated by the late-stage functionalization of complex bioactive molecules.*

Pyridine is a prevalent structural motif present in numerous natural products, pharmaceuticals, and functional materials.[1] Accordingly, considerable effort has been directed towards expedient access to an array of diverse pyridine structures. Among them, the photocatalyzed chemical modification of the pyridine core has attracted much attention.[2] However, the pyridine scaffold contains multiple reactive sites, and site-selective functionalization in radical additions remains a long-standing challenge.[3] Recently, the remote radical (hetero)-aryl migration strategy has proven to be a powerful tactic for the efficient construction of structurally complex target molecules by providing a new synthetic toolbox to deal with the elusive radical transformations.[4] For example, Zhu and co-workers highlighted the power of distal heteroaryl *ipso*-migration, leading to various chemical transformations with an excellent functional-group tolerance (Scheme 1 a).[5] Despite the significant advances reported in the field thus far, the scope of this platform is mainly limited to *ipso*-substitution reactions or migration (i.e., the radical Smiles–Truce rearrangement).[6] A new successful strategy that enables the incorporation of pyridyl groups by *ortho*-selective migration would significantly broaden the potential of remote functionalizations by overriding the commonly observed preference for the site selectivity.



Scheme 1. Design plan: Site-selective alkene trifluoromethyl-pyridylation by remote *ortho*-selective migration.

The potential of N-alkoxypyridinium salts has been demonstrated in synthesis as easily accessible, versatile, and bench-stable pyridine surrogates.[7–9] For example, cobalt-mediated alkene functionalization[8] and a remote C(sp^3)–H pyridylation strategy by 1,5-hydrogen atom transfer[9] were successfully achieved using N-alkoxyheteroarenium salts to afford various alkylpyridine products. Unfortunately, only modest regioselectivity (C2 vs. C4) has been observed in the trapping of N-alkoxypyridinium salts with secondary alkyl radicals while tertiary alkyl radicals provide *para*(C4)-selective pyridyl products (Scheme 1 b).

To overcome the regioselectivity issues, we envisioned the possibility of a controlled migration of a remote group to the *ortho*-position of the pyridyl ring to afford C2-substituted pyridyl derivatives. In our design, an electrophilic CF_3 radical would chemoselectively react with the alkene over a pyridinium salt to provide an alkyl radical intermediate.[10] This process sets the stage for group migration to the *ortho*-position if the resulting tethered nucleophilic alkyl radical would engage in an intramolecular *endo* addition onto the C2-position of pyridinium salt.[11] Subsequent cleavage of the N–O bond delivers C2-fluoroalkylated pyridine derivatives, as outlined in Scheme 1 c.[12]

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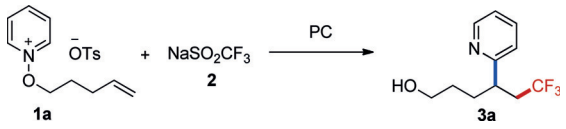
To explore such a strategy, we designed N-alkenyloxypyridinium salts as starting substrates for the difunctionalization of alkenes with concomitant pyridyl-group migration. Despite this inspiration, the crucial challenge in this proposed approach may lie in the competitive fragmentation of the N-alkoxypyridinium salts by single-electron transfer (SET), leading to the formation of alkoxy radicals and pyridines.[13] Therefore, a successful photocatalytic system using this approach requires the selective generation of radicals to promote the group migration to the *ortho*-position of the pyridyl ring, while minimizing the competing process of N–O bond cleavage to prevent undesired reactions, exemplified by alkoxy radical cyclization.[14] Herein, we report the successful realization of a trifluoromethylative pyridylation of alkenes through an *ortho*-selective migration strategy. Notably, this strategy enables not only secondary, but also tertiary alkyl radicals to react with the C2-position of pyridinium salts, overriding the commonly observed preference for the C4-addition. Moreover, the utility of the current method was further expanded by successfully applying it to the reaction with P-centered radicals.

In line with our hypothesis, the feasibility of the proposed *ortho*-selective migration was investigated using the N-alkoxypyridinium salt **1a** (Table 1) as a model substrate under blue LED irradiation. In the absence of the CF_3 radical source, illuminating a photocatalyst such as the 3-phosphonated quinolinone $\mathbf{Q_1}$[15] or Eosin Y (EY) enables the formation of the alkoxy radical that triggers a competing intramolecular alkoxy radical cyclization with an alkene and subsequent pyridylation, leading to the formation of pyridine-tethered tetrahydrofuran (see the Scheme S7 in the Supporting Information for details).[14] We next examined the use of the Langlois reagent **2** as a CF_3 radical source by a reductive quenching photocatalytic cycle.[16] To our delight, the desired product **3a** was formed through trifluoromethylative *ortho*-selective pyridyl migration when $\mathbf{Q_1}$ was used as a photocatalyst (entry 1, 33% yield), highlighting that the proposed overall process can be achieved effectively. The results revealed that the dissociation of the N–O bond in **1a** could be minimized in the presence of $NaSO_2CF_3$ (see the Scheme S7 for details). A variety of CF_3 radical sources were screened to obtain the maximum yield, and the yield of **3a** was significantly lower using other CF_3 radical sources (see Table S1 for details). Among the solvents screened, DMSO was most efficient for this reaction. Following extensive optimization, we found that the reaction occurred even more efficiently by using EY ($E_{red} = 0.83$ V vs. SCE)[17] as a photocatalyst (entry 8, 70% yield). In addition, we surveyed the counterions of the pyridinium salt and found that TsO^- provided optimal yields (see Table S1 for details). A series of control experiments confirmed that the reaction did not proceed in the absence of photocatalyst or visible light (entries 9 and 10).

Table 1: Optimization of the reaction conditions.[a]



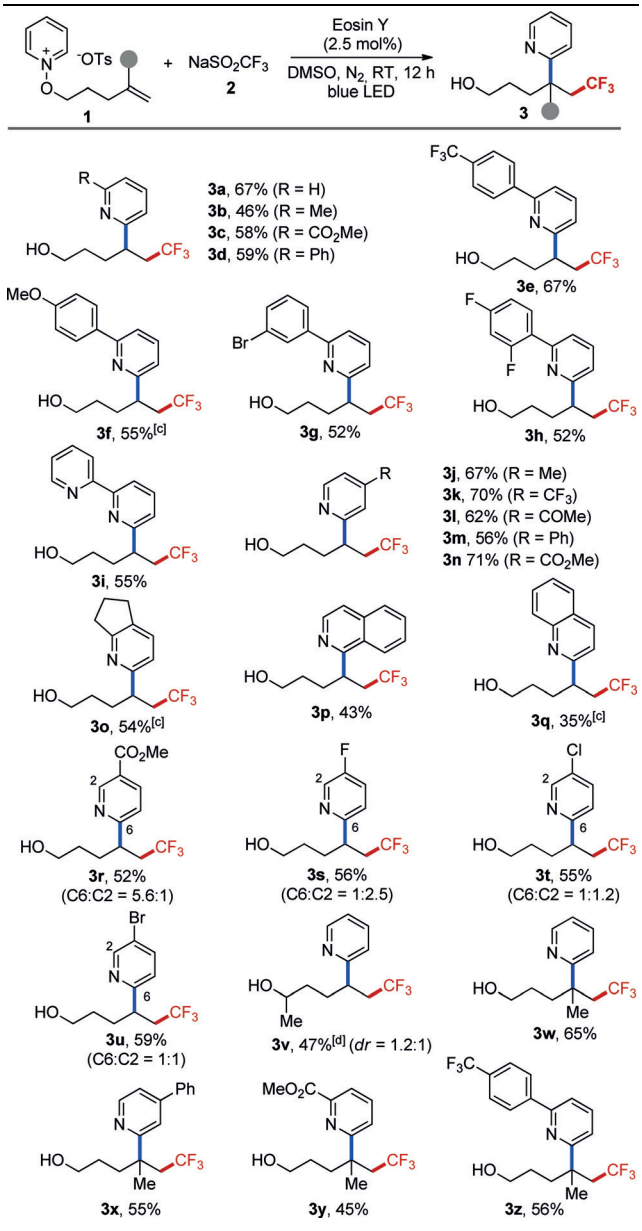
Entry	Photocatalyst	Solvent	Yield [%][b]
1	$\mathbf{Q_1}$	DCM	33
2	$\mathbf{Q_1}$	MeCN	59
3	$\mathbf{Q_1}$	DMSO	66
4	*fac*-Ir(ppy)$_3$	DMSO	60
5	[IrdF(CF$_3$)ppy$_2$bpy]PF$_6$	DMSO	58
6	Ru(phen)$_3$Cl$_2$·*x*H$_2$O	DMSO	59
7	Mes-Acr$^+$	DMSO	24
8	Eosin Y	DMSO	70
9[c]	Eosin Y	DMSO	0
10	–	DMSO	trace
11[d]	Eosin Y	DMSO	trace

[a] Reactions were performed with mixtures of **1a** (0.2 mmol), **2** (0.4 mmol), and PC (2.5 mol%) in solvent (2.0 mL), irradiating with a blue LED (440 nm, 8.5 W) under N_2 at RT for 12 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture. [c] The reaction was carried out in the dark. [d] TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 2.0 equiv) was added.

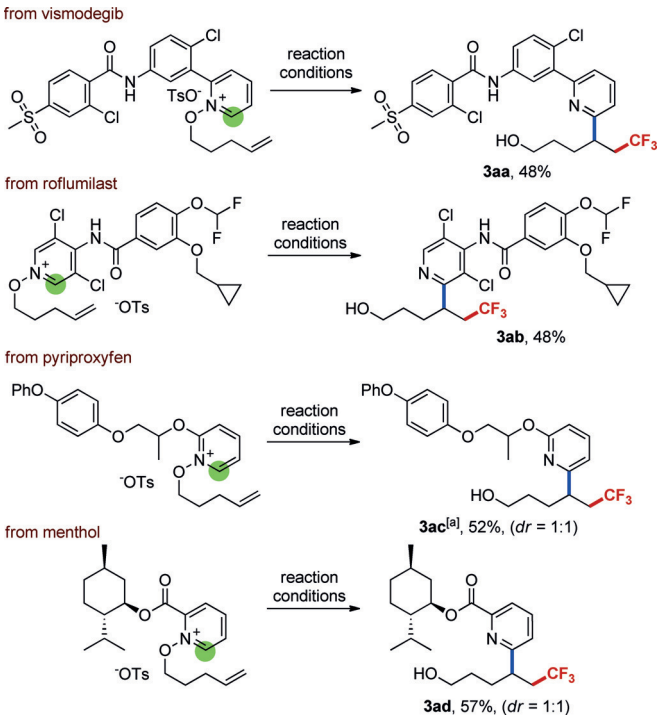
Having identified the optimized reaction conditions, we investigated the generality of this method as illustrated in Table 2. A wide range of pyridinium substrates bearing various functional groups such as methyl, ester, and substituted aryl groups (methoxy, bromo, fluoro, and trifluoromethyl) at the C2-position are selectively alkylated at the C2-position of pyridine scaffolds to afford the desired products (**3a–h**). Substrates with C4-substituents such as methyl (**3j**), trifluoromethyl (**3k**), ketone (**3l**), phenyl (**3m**), and ester (**3n**) were also successfully applied to this method. The reactions with C3-substituted pyridinium salts proceeded to afford the desired products as mixtures of C2- and C6-alkylated pyridines (**3r–u**), and none of the *para*(C4)-substituted product was detected. These results indicate that the products were formed by intramolecular *ortho*-selective migration. The installation of *ortho*(C2)-substituted pyridyl groups at the quaternary centers is quite challenging because tertiary radicals generally tend to add preferentially at the C4-position of pyridinium salts to provide C4-pyridylated products.[8,9] Impressively, this strategy was not limited to secondary alkyl radical intermediates but could also be successfully extended to tertiary radicals to forge quaternary carbon centers bearing *ortho*-substituted pyridyl groups with excellent C2 selectivity (**3w–z**). In addition, the scope could be expanded to a secondary alkoxy structure, which afforded the corresponding secondary alcohol product **3v**. We subsequently investigated the utility of our method by exploring other heteroarenes. Substrates containing bipyridine, isoquinoline, and quinoline were well tolerated and provided the corresponding products **3i**, **3p**, and **3q**.

To further underline the broad applicability, we attempted late-stage modifications of pharmaceutically relevant molecules. As depicted in Scheme 2, structurally complex substrates derived from pyridine-based drugs with various functional groups such as vismodegib, roflumilast, pyriproxyfen, and menthol were subjected to the optimized reaction conditions, and the C2-fluoroalkyl-functionalized pyridines **3aa–ad** were formed with good functional-group tolerance. Therefore, this *ortho*-selective migration strategy represents an attractive synthetic tool for rapidly accessing a wide range of valuable C2-fluoroalkyl-functionalized pyridine motifs

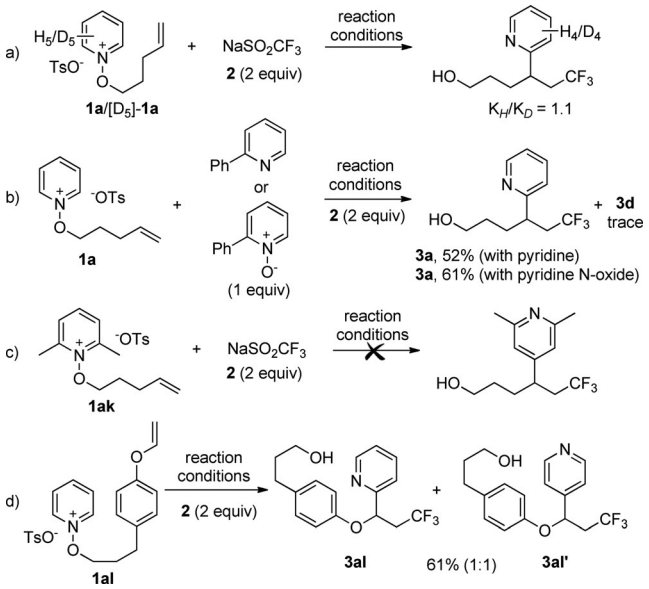
Table 2: Exploration of substrate scope.[a,b]



[a] Reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol), and EY (2.5 mol%) in DMSO (2.0 mL), irradiating with a blue LED (440 nm, 8.5 W) under N_2 at RT for 12 h. [b] Yield of isolated product. [c] $NaSO_2CF_3$ (5 equiv) was used. [d] The reaction was conducted for 6 h.



Scheme 2. Site-selective late-stage functionalization of complex molecules by *ortho*-selective migration. $Ru(phen)_3Cl_2{\cdot}xH_2O$ (2.5 mol%) and $NaSO_2CF_3$ (5 equiv) were used. [a] Eosin Y (2.5 mol%) and $NaSO_2CF_3$ (5 equiv) were used.



Scheme 3. Control experiments.

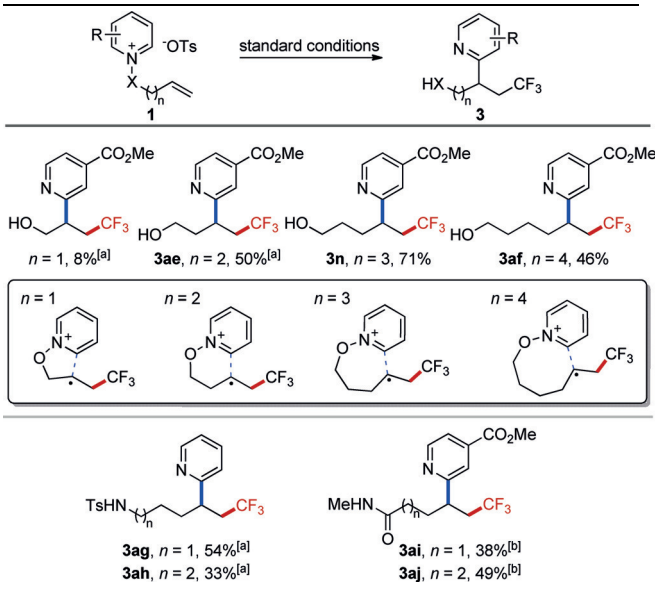
with potential applications in the construction of compound libraries and the late-stage functionalization of medicinally relevant compounds.

To gain insight into the reaction mechanism, we conducted a series of control experiments (Scheme 3). First, the Stern–Volmer plots of fluorescence data exhibit that the EY* excited state is quenched by both the Langlois reagent and N-alkenyloxypyridinium. The quenching was found to be linearly dependent on the concentration of the Langlois reagent and pyridinium salt (see the Figures S3 and S4 for details). Kinetic isotope effect (KIE) experiments were carried out with the substrate [D_5]-**1a**, in which the K_H/K_D ratio was found to be 1.1, indicating that the deprotonation step is not significantly involved in a rate-determining step. When a mixture of **1a** and 2-phenylpyridine (or 2-phenylpyridine N-oxide) were subjected to the standard reaction conditions, only **3a** was observed, showing that alkylation occurred only at pyridinium salt (Scheme 3b). To better understand the *ortho*-selective migration pathway, the 2,6-dimethyl-substituted pyridinium salt **1ak** was used as a sub-

strate. Notably, no desired product was detected (Scheme 3c), and indicates that intramolecular radical addition to the C2 position of the pyridinium salt is involved to provide the products. Additionally, we noticed that the reaction of the substrate **1al** gave a mixture of products (C2/C4 = 1:1), implying that a long-chain linker is required to access to the C4 position of the pyridine core in an intramolecular fashion (Scheme 3d).

To better understand the migration pathway, a series of substrates containing different alkyl-chain lengths were investigated (Table 3). The desired products could be successfully obtained from the substrates ($n = 2, 3, 4$), indicating that the *ortho*-selective migration favorably proceeded by six-,

Table 3: Exploration of the scope with respect to the alkyl chain.

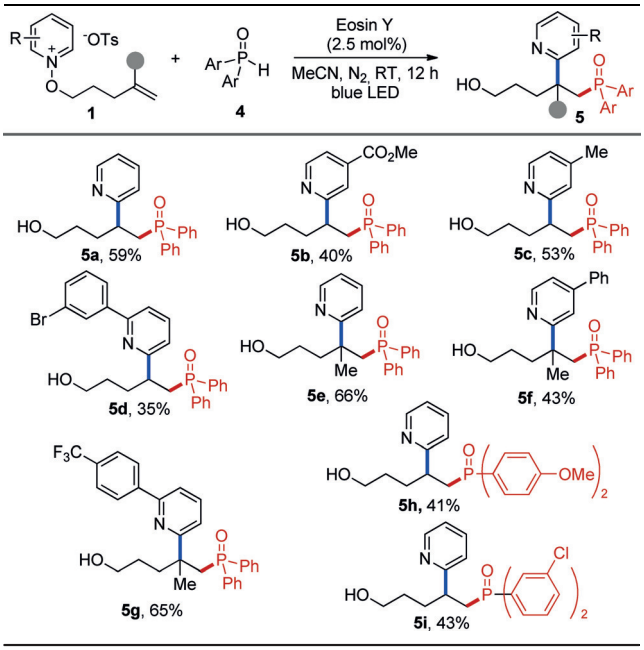


[a] $NaSO_2CF_3$ (5 equiv) was used. [b] MsO^- was used for **1** instead of TsO^-.

seven-, and eight-*endo* addition to afford the corresponding products **3ae**, **3n**, and **3af**. It is noteworthy to emphasize the breakthrough in long-distance radical migration, especially via an eight-membered cyclic transition state. Moreover, this method could be extended to the interesting examples of N-amidopyridinium substrates bearing sulfonamide (**3ag** and **3ah**) or carboxamide chains (**3ai** and **3aj**), effectively yielding the corresponding products.

We next turned our attention to explore P-centered radicals, as illustrated in Table 4. To our delight, phosphinoyl radicals preferentially react with the alkene moiety of N-alkoxypyridinium salts, enabling *ortho*-selective migration to install pyridyl and phosphorus groups. A series of pyridinium salts bearing various functional groups, such as ester (**5b**), methyl (**5c**), 3-bromophenyl (**5d**), and 4-trifluoromethylphenyl (**5g**), were successfully employed to generate the corresponding products. In a similar fashion, the reaction was further extended to tertiary radicals to construct quaternary carbon center (**5e**–**g**). The scope of the phosphine oxides was next evaluated and worked well to furnish the corresponding products **5h** and **5i**.

Table 4: Scope of the *ortho*-selective migration using P-centered radicals.[a,b]



[a] Reactions were performed with **1** (0.1 mmol), **2** (0.2 mmol), and EY (2.5 mol%) in MeCN (1.0 mL), irradiating with a blue LED (440 nm, 8.5 W) under N_2 at RT for 12 h. [b] Yield of isolated products.

The photoexcited state EY* under blue LED irradiation undergoes a single-electron oxidation with the Langlois reagent to yield an electrophilic CF_3 radical, which subsequently reacts with the alkene (Figure 1). Afterward, the nucleophilic alkyl radical is disposed to undergo intramolecular radical addition to the C2-position of the pyridinium substrate to form the radical cation species, which undergoes deprotonation and subsequent N–O bond cleavage to form the alkoxy radicals. The resultant radical can initiate a radical-chain pathway that is quite productive, considering a relatively high quantum yield ($\Phi = 5.1$). In the process, an alternate reaction pathway involving reduction by SET events in the photoredox catalytic cycle can be envisioned to maintain the catalytic cycle.

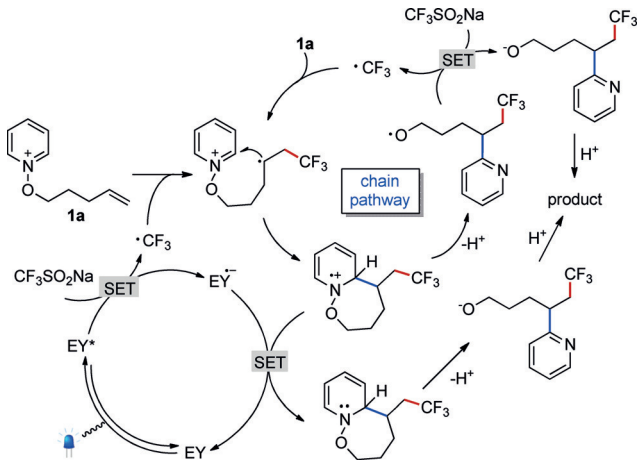


Figure 1. Plausible reaction mechanism.

In summary, a visible-light-induced site-selective trifluoromethylative pyridylation of alkenes has been achieved by an unprecedented remote pyridyl *ortho*-selective migration to afford synthetically valuable C2-fluoroalkyl-functionalized pyridines. This strategy features a photoredox radical process involving a sequential formation of a CF_3 radical, the addition of the CF_3 radical to the alkene, and an intramolecular *endo* addition to the *ortho*-position of the pyridinium salt. Notably, this method could be successfully extended to tertiary radicals to forge quaternary carbon centers bearing *ortho*-substituted pyridyl groups with excellent C2 selectivity. Moreover, the method could be successfully applied to the reaction with P-centered radicals in these systems.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · heterocycles · photochemistry · radicals · reaction mechanisms

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